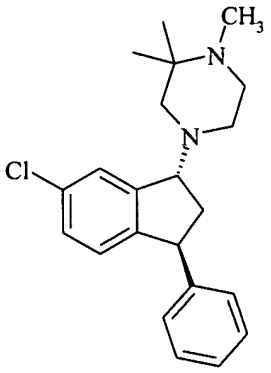
Claims

1. A succinate salt or a malonate salt of the compound of formula (I)



(I)

[*trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine].

2. The succinate salt according to claim 1, which is the hydrogen succinate salt of the compound of formula (I).

3. A crystalline hydrogen succinate salt of Compound I defined in claim 1.

4. The salt of claim 3, which is crystal form alpha.

5. The salt of claim 3 or 4, which crystal form is characterized by an X-Ray powder diffractogram corresponding to that of Figure 1.

6. The salt of any of claims 3-5, which crystal form is characterized by an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) showing peaks at the following 2θ-angles: 9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; 29.65.

7. The salt of any of claims 3-6, which crystal form is characterized by having a DSC trace showing an endotherm with onset about 139-141°C.

8. The malonate salt according to claim 1, which is the hydrogen malonate salt of the compound of formula (I).

9. A crystalline hydrogen malonate salt of Compound I as defined in claim 1.

10. The crystalline salt of claim 9, which crystal form is characterized by an X-Ray powder diffractogram shown in Figure 3.

11. The crystalline salt of claim 9 or 10, which crystal form is characterized by an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) showing peaks at the following 2θ-angles: 8.3; 10.6; 11.5; 12.8; 14.2; 14.5; 14.7; 15.8; 16.5; 17.4; 17.6; 18.0; 18.6; 19.2; 21.2; 22.0; 22.9; 23.7; 24.7; 28.8

12. A pharmaceutical composition comprising a salt according to any of claims 1-11 together with at least one pharmaceutically acceptable carrier, filler or diluent.

13. A salt according to any of claims 1-11 for use in medicine.

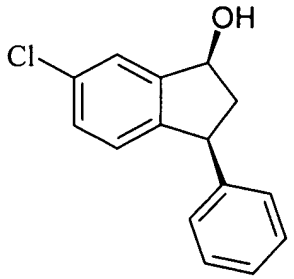
14. Use of a salt according to any of claims 1-11 in the preparation of a medicament for the treatment of a disease selected from the group consisting of a disease involving psychotic symptoms, anxiety disorders, affective disorders including depression, sleep disturbances, migraine, neuroleptic-induced parkinsonism, or abuse disorders, *e.g.* cocaine abuse, nicotine abuse, or alcohol abuse.

15. Use of a salt according to any of claims 1-11 in the preparation of a medicament for the treatment of schizophrenia or other psychotic disorders.

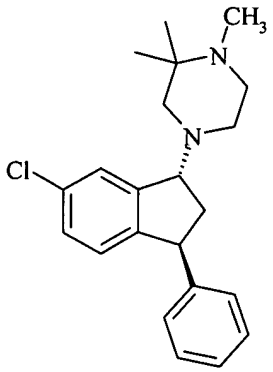
16. Use of a salt according to any of claims 1-11 in the preparation of a medicament for the treatment of a disease selected from the group consisting of Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder, and mania in bipolar disorder.

17. Use of a salt according to any of claims 1-11 in the preparation of a medicament for the treatment of one or more of: positives symptoms, negative symptoms and depressive symptoms of schizophrenia.

18. A method for manufacturing 4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (formula I) or a salt thereof, which method comprises conversion of the compound of formula Va in *cis*-configuration to the compound of formula I, wherein formula I and Va are as follows:

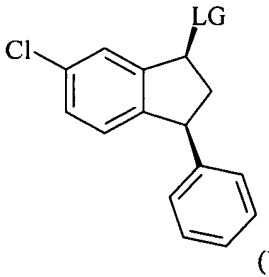


(Va)



(I)

19. The method of claim 18, comprising conversion of the alcohol group of the cis-alcohol of formula Va to a suitable leaving group LG resulting in the compound of formula VI.



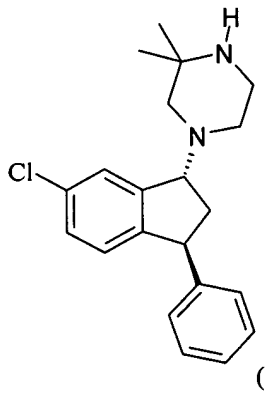
(VI)

20. The method of claim 19, wherein LG is a halogen, *e.g.* Cl or Br, preferably Cl or a sulphonate.

21. The method of claim 19 or 20, wherein Compound VI is precipitated from a suitable solvent.

22. The method of claim 21, wherein LG is a halogen, preferably Cl, and the solvent is an alkane, e.g. heptane.

23. The method of any of claims 19-22, wherein Compound VI is reacted with 2,2-dimethylpiperazine to obtain the compound of formula VII.



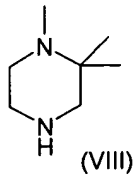
(VII)

24. The method of claim 23 comprising methylation at the secondary amine to obtain the free base of the compound of formula I.

25. The method of claim 23 or 24, wherein the compound of formula VII is precipitated as a suitable salt, *e.g.* a salt of an organic acid, such as an organic diacid.

26 The method of claim 25, wherein the formed salt is the hydrogen fumarate salt or the hydrogen maleate salt of Compound VII.

27. The method of any of claims 19-22, wherein compound VI is reacted with 1,2,2-trimethylpiperazine (formula VIII) to obtain the free base of the compound of formula (I).

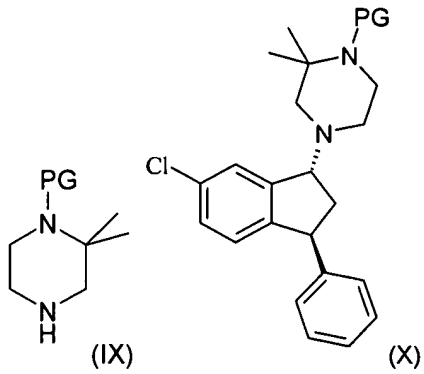


(VIII)

28. The method of any of claims 20-24, comprising

- reacting Compound VI with 1-protected 2,2-dimethylpiperazine (IX), wherein PG is a protection group, thereby obtaining a compound of formula X; and
- deprotecting Compound X to obtain Compound VII or converting Compound X directly to Compound I,

wherein Compound IX and X are as follows:

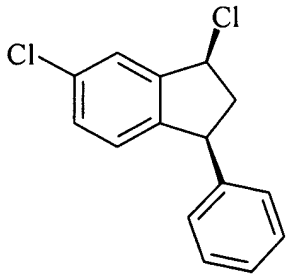


(IX) (X)

29. The method of claim 28, wherein the protection group PG is selected from the group of phenylmethoxycarbonyl, tert-butyloxycarbonyl, ethoxycarbonyl, and benzyl.

30. A method for the preparation of the compound of formula I or a salt thereof comprising reacting a compound of formula VIa (i.e. Compound VI for which LG is Cl) with 2,2-dimethylpiperazine thereby obtaining the compound of formula VII, followed by methylation at the secondary amine.

31. A method for the preparation of a compound of formula I or a salt thereof comprising reacting a compound of formula VIa (i.e. Compound VI for which LG is Cl)



(VIa)

with 2,2-dimethylpiperazine in presence of a base, followed by reductive amination with suitably reagents, such as formaldehyde, paraformaldehyde, trioxane or diethoxymethane followed by isolation of the compound of formula I as the free base or as a salt thereof.

32. A method for manufacturing 4-((1*R*,3*S*)-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (formula I) or a salt thereof, which method comprises conversion

of the compound of formula VII to the compound of formula I, wherein formula VII is as defined in claim 23.

33. The method of any of claims 18-32, wherein the compound of formula (I) is precipitated as a suitable salt, *e.g.* a salt of an organic acid, such as an organic diacid, in order to remove undesired *cis* diastereoisomer.

34. The method of claim 34, wherein the formed salt is a hydrogen fumarate salt of Compound I.

35. The method of any of claims 18-34, comprising preparing the succinate salt defined in any of claims 1-7.

36. The method of claim 35, wherein the Compound I hydrogen succinate is prepared in a ketone solvent, preferably acetone, e.g. aqueous acetone.

37. The method of any of claims 18-34, comprising preparing the malonate salt defined in claim 1 or any of claims 8-11.

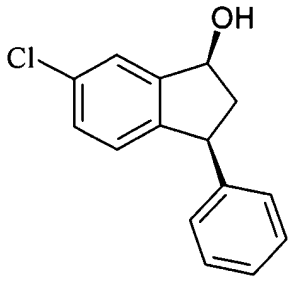
38. The method of claim 37, wherein the Compound I hydrogen malonate is prepared in a in a alcohol solvent, e.g. 2-propanol.

39. The method of any of claims 18-38 comprising conversion of the free base of the compound of formula (I) to a salt as defined in any of claims 1-14.

40. The method of any of claim 39, wherein the base of formula (I) obtained is first isolated as the fumarate salt thereof, which is optionally recrystallised one or more times, the fumarate salt is then treated with a base to liberate the free base of the compound of formula (I) which is then converted to the succinate or malonate salt thereof.

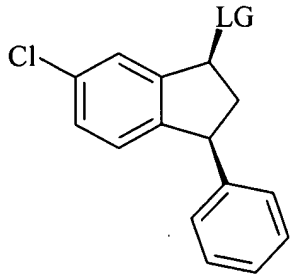
41. The method of any of claims 18-39 followed by isolation of the compound of formula I as the free base or as a salt thereof, e.g. as a succinate salt as defined in any of claims 1-7 or as a malonate salt as defined in any of claims 8-11.

42. A compound (Va) having the structure:



(Va)

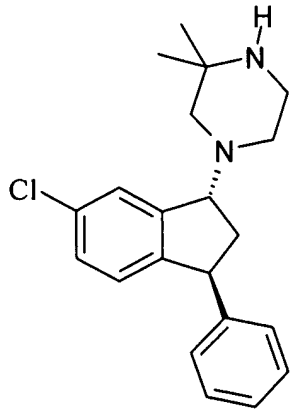
43. A compound (VI) having the structure:



(VI)

wherein LG is a potential leaving group, e.g. selected from the group consisting of a halogen, *e.g.* Br or Cl, preferably Cl, or a sulphonate.

44. A compound (VII) having the structure as follow:



(VII)

or a salt thereof.

45. A compound as defined in any of claims 42-44, which compound is substantially pure.

46. The method of any of claims 18-31 or any of claims 33-41, wherein Compound Va is obtained by enzymatical resolution of Compound V.